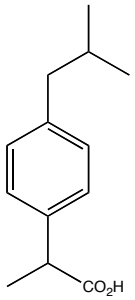
**CH241 Experiment #3 – Weeks of October 9 and 26, 2018**

**Chemical Resolution of Racemic Ibuprofen Using a Chiral Amine***

***(Please let your laboratory instructor know if you are allergic to ibuprofen)***

## Introduction

Ibuprofen (**1**) is a chiral carboxylic acid that belongs to a class of pharmaceuticals known as non-steroidal anti-inflammatory drugs (NSAIDs). It is an active component in several over-the-counter medicines, such as Motrin® and Advil®. The active form is (S)-ibuprofen, although the inactive *R*-form is slowly converted into the *S*-enantiomer in the body. Ibuprofen is generally sold as a racemic mixture, but it appears that formulations containing just the *S*-isomer are more effective. Thus, there have been efforts to prepare and/or isolate just the active enantiomer of ibuprofen.[1] In the first week of this two-week laboratory, you will react the chiral base (*S*)-(-)-α-phenylethylamine (**2**) with a racemic ibuprofen mixture to form a pair of diastereomeric salts that can be separated based on their different solubilities in water. In the second week, you will recover enantiomerically pure (*R*)- and (*S*)-ibuprofen and determine the optical rotation of each of these compounds.

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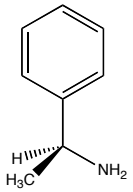


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## Week 1: Isolation of (*S*)-Ibuprofen

### Procedure

**Step 1**: In a 100 mL round-bottom flask equipped with a thermometer, combine 3.0 g of racemic ibuprofen with 30 mL of aqueous 0.24 *M* KOH. Heat this mixture with stirring until the internal temperature of the liquid is between 75 and 85 °C. By then most of the ibuprofen should have dissolved as its potassium salt. To this hot solution, carefully add dropwise 0.9 mL of (*S*)-(-)-α-phenylethylamine. (This amine reacts with atmospheric $CO_2$ so please minimize its exposure to air.) Continue to stir while maintaining the same temperature for 45 min. Then remove the flask from the heat source, let it cool to room temperature, and vacuum filter the mixture. Save the filtrate in a clearly labeled container for next week. Wash the solid with 2-3 mL of ice-cold water and then use it in step 2.

**Step 2**: Place your solid in a 50 mL beaker. Add 25 mL of 2 *M* $H_2SO_4$ and stir with a magnetic stir bar for 5 minutes. Carefully pour the contents of the beaker into a 125 mL separatory funnel and extract with 15 mL of methyl-*tert*-butyl ether (MTBE). Repeat this extraction two more times by pouring your aqueous layer back into the separatory funnel, adding 15 mL additional MTBE, and re-extracting. Combine all three MBTE layers and, in the same separatory funnel, wash once with water (15 mL) and once with brine (15 mL). Dry the organic layer with anhydrous sodium sulfate, decant your dried organic layer into a round bottom flask, and remove the solvent using a rotary evaporator. Transfer the residue to a vial, weigh, and label it as (*S*)-ibuprofen.

**Week 2: Isolation of (*R*)-Ibuprofen and Polarimetry**

**Step 1**: Transfer the filtrate you saved from Week 1 into a 100 mL flask. Carefully add 25 mL of 2 *M* $H_2SO_4$ and stir for 5 min. Pour the contents of the beaker into a 125 mL separatory funnel and extract with 15 mL of MTBE. Repeat this extraction two more times. Combine all three MBTE layers and, in the same separatory funnel, wash once with water (15 mL) and once with brine (15 mL). Dry the organic layer with anhydrous sodium sulfate, decant your dried organic layer into a round bottom flask, and remove the solvent with a rotary evaporator. Transfer the residue to a vial, weigh, and label it as (*R*)-ibuprofen.

**Step 2**: Dissolve 100 to 300 mg of each enantiomer of ibuprofen **separately** in 2 mL of ethanol. Be sure to accurately record the weights. Transfer the ethanol solutions of each enantiomer into **separate** 10 mL volumetric flasks. Carefully make up the volume to 10 mL in each case. Determine the optical rotation of each solution and calculate the specific rotation and optical purity of each enantiomer.

$$\% \text{ Optical purity} = \frac{\text{specific rotation of sample}}{\text{specific rotation of pure enantiomer}} \times 100$$

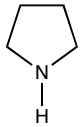
**Prelab – Week 1**
**(Due in lab week of October 9)**

1. In an organic laboratory text or on the internet, read and take notes about extraction, the use of a separatory funnel, and use of drying agents (for drying organic solvents after extraction).
2. Look up and record the specific optical rotations of the two enantiomers of ibuprofen.
3. Carefully read section 4.9 of your textbook (this will also help you answer #4 and #5, below).
4. Draw structures for the two salts obtained when racemic ibuprofen reacts with (*S*)-(-)-α-phenylethylamine. Clearly explain why these salts are diastereomeric.
5. Prepare a flow chart that clearly shows the strategy for resolving racemic ibuprofen by reacting it with (*S*)-(-)-α-phenylethylamine. *A clear understanding of your separation strategy is cricital to understanding the experiment!*

**Prelab – Week 2**
**(Due in lab week of October 26)**

1. In your organic laboratory text, read and take notes on the technique of polarimetry (sections 4.4-4.5).

2. Had you used the base shown below (instead of (*S*)-(-)-α-phenylethylamine), could you have successfully resolved racemic ibuprofen? Clearly explain your reasoning.



3. Would you be able to distinguish the two enantiomers of ibuprofen based on their melting points? How about their $R_f$ values on silica TLC plates (like those you used in Experiment 1) using an appropriate solvent?

## WHAT SHOULD BE IN YOUR NOTEBOOK?

1. The usual items: an entry of the title, date, and page number in your table of contents and the title, date, and partner's name all pages of your experiment.
2. Brief descriptions of the procedures you followed in each step along with the masses and volumes of materials that you used.
3. Yield of the two enantiomers of ibuprofen.
4. Calculation of specific rotations and optical purity.

## WHAT SHOULD BE IN YOUR LABORATORY REPORT?

Use the **Experiment 3 Report Form** to write your lab report.

**Remember to:**

1. Submit an electronic copy to CH241Lab@colby.edu by the date your report is due.
2. Submit a hardcopy in lab on the due date (start of lab).

[1]Based on: McCullagh, J. V. *J. Chem. Ed*, **2008**, *85*, 941.